PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Bethany A. JANOWSKI and
David John MANGELSDORF

Serial No.: 09/603,131

Filed: June 23, 2000

For: NOVEL OXY-STEROL LIGANDS FOR THE LXR RECEPTOR AND USES THEREOF

Group Art Unit: 1646

Examiner: M. PAK

Atty. Dkt. No.: UTSD:578USC2/SLH

BRIEF ON APPEAL

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37 C.F.R. §1.8

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November 17, 2003
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Steven L. Highlander

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APPEAL BRIEF

BOX AF
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellant hereby submits an original and two copies of this Appeal Brief to the Board of Patent Appeals and Interferences in response to the Final Office Action dated February 10, 2003. This brief is due on November 15, 2003, by virtue of the Notice of Appeal received by the U.S. P.T.O. on July 15, 2003, and the enclosed Petition for Extension of Time and related fee. The fee for filing this Appeal Brief is also attached hereto. Should any other fees be due, or the attached fees be deficient or absent, the Commissioner is authorized to withdraw the appropriate fee from Fulbright & Jaworski Deposit Account No. 50-1212/UTSD:578USC2/SLH. Please date stamp and return the enclosed postcard to evidence receipt of this document.

I. Real Parties in Interest

The real parties in interest are the assignee, Board of Regents, University of Texas System, Austin, TX, and the licensee, X-Ceptor Therapeutics, Inc., San Diego, CA.

II. Related Appeals and Interferences

There are no interferences or appeals for related cases.

III. Status of the Claims

Claims 1-15 were filed with the original application; claims 16-23 were added. Claims 2, 3, 6, 9-16 and 19 have been canceled. Thus, claims 1, 4, 5, 7, 8, 17, 18, 20-23 are rejected and are appealed. A copy of the rejected claims is attached as APPENDIX 1 to this brief.

IV. Status of Amendments

An amendment is being filed concurrent with this brief in order to reduce the number of issues on appeal. However, given that the amendment has not yet been entered, APPENDIX 1 will list the claims as presently pending. Should the examiner enter the amendments, appellants will provide an updated copy of the claims in their Reply Brief.

V. Summary of the Invention

The present invention provides a method of screening for agonists of an oxysterol activator of LXRα transcription, comprising the steps of: introducing a reporter construct and an LXR expression construct into a host cell; treating the host cell with potential LXR-specific ligands; and identifying compounds which activate LXRα transcription. Specification at page 5, lines 3-8.

VI. Issues on Appeal

Are the claims definite under 35 U.S.C. §112, second paragraph?

Are the claims enabled under 35 U.S.C. §112, first paragraph?

Are the claims anticipated under 35 U.S.C. §102(b) by Willy *et al.* (Exhibit A)

Are the claims anticiapted under 35 U.S.C. §102(b) by Hogness *et al.* (Exhibit B)?

VII. Grouping of the Claims

The claims do not stand and fall together, as discussed in §IX.C, below.

VIII. Summary of the Argument

As has been pointed out repeatedly, the terms LXRα (whether referring to expression constructs or proteins themselves) and oxysterols were commonly used at the time the present application was filed, as demonstrated by references of record. Thus, the claims are not indefinite.

It also is untrue that it would require undue experimentation to make and use the claimed invention in light of the extensive disclosure provided in the specification. Not only is there extensive discussion of how to make and use mammalian expression constructs, but there also are examples of doing just that. A proper *Wands* analysis therefore ***supports*** appellants' position regarding enablement.

Finally, the anticipation rejections are improper. As discuss, Willy *et al.* does not describe screening oxysterols, it describes retinoids, which are distinct. Hogness *et al.* presents an even more distant issue, as the insect ecdysteroid receptor disclosed therein cannot be confused with the LXRα of the present invention.

IX. Argument

1. Rejections Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 1, 4, 5, 7, 8, 17, 18 and 20-23, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse the rejection based on the grounds that the currently pending claims both particularly point out, and distinctly claim the subject matter that Applicants consider their invention.

LXRα expression construct and protein: Appellants traverse the Examiner's assertion that "LXRα" is indefinite. As the Examiner has acknowledged, the human LXRα gene was disclosed in the Willy *et al.* paper over a year prior to appellants' priority date, and the sequence of human LXRα was publicly available, for example, via GenBank (Accession No. U22662), at the time the present application was filed. Accordingly a person of ordinary skill in the art would immediately recognize what is meant by the term "LXRα."

In addition, in order to reduce issues and expedite prosecution, and amendment to claims 1, 20, and 21 is offered reciting the use of a ***human*** LXRα expression construct, which encodes for the expression of a human LXR α protein. Applicants thus request withdrawal of the above rejection in light of these arguments and the amendments to the claims.

Oxysterol activator: The Examiner again argues that this term is not defined or limited by structure. Both of these assertions are incorrect. First, an oxysterol is a well-defined chemical term that literally means "oxygenated sterol." *See* Gibbons, G.F., "The role of oxysterols in the regulation of cholesterol biosynthesis," *Biochem. Soc. Trans.* 11,

649-651, 1983 (Exhibit C); and Parish *et al.*, "Oxysterols: chemical synthesis, biosynthesis, and biological activities," *Lipids* 21, 27-30, 1986 (Exhibit D). Second, the specification provides a number of examples ("... said oxysterol selected from the group consisting of 22(R)-hydroxycholesterol, 20(S)-hydroxycholesterol, 24-hydroxycholesterol, and 25-hydroxycholesterol, 7α-hydroxycholesterol, and FF-MAS") of what this term means such that if there were doubt about the "metes and bounds" of this term, the examples would provide clarification. See specification at page 5, lines 17-23. And third, the specification references an article by Russell (C25) (Exhibit E) that further characterizes this class of compounds. Specification at page 4, lines 11-13.

Taken together, in light of the relevant legal standards, this evidence refutes the Examiner's position, which is based on pure speculation. Reversal of the rejection by the Board is respectfully requested.

2. Rejection Under 35 U.S.C. §112, First Paragraph

Claims 1, 4, 5, 7, 8, 17, 18, and 22-23 have been rejected under 35 U.S.C. §112, first paragraph as allegedly not being enabled for the claimed methods because the LXRα is allegedly "defined only by function which is not defined in the specification." Applicants respectfully traverse the rejection on the grounds that the currently pending claims are fully enabled by the present specification.

The Examiner contends that the specification does not enable the claimed methods of screening for oxysterol activators of LXRα. The Examiner further contends that the specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants respectfully disagree and point to the Examples on pages 16-24 of the application and the drawings (FIGS. 1-5), which provide explicit instructions for the creating of expression constructs, reporter constructs as well as methods for performing the screens.

Applicants specifically highlight example 1, page 16 lines 24 to 26 and page 17 lines 1 to 23, for disclosures enabling the construction of reporter and expression constructs. Further, Example 1 provides a complete and accurate description of the human LXRα construct used in the claimed methods based on a publicly available reference, which discloses the entire sequence, and GenBank Accession No., of human LXRα.

Second, in contrast to the Examiner's assertion, a person of ordinary skill in the art would not be required to undertake undue experimentation to make and use the full scope of the claimed invention.

Applicants cite *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) for the proposition that the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art (see also, MPEP §2164.03). Applicants respectfully assert that methods of sub-cloning known genes between well known mammalian expression constructs was well within the purview of a molecular biologist of ordinary skill in the art, and therefore the exact sequence need not be provided because it was already publicly available.

For the above reasons, Applicant respectfully traverse Examiner's rejection under 35 U.S.C. §112, first paragraph for lack of enablement.

Applicants also respectfully traverse the Examiner's contention that the specification allegedly necessitates undue experimentation. The correct standard for determining undue experimentation is an analysis based on the six factors presented in *In re Wands* (858 F.2d at 731,737, 8 USPQ2d at 1400, 1404 (Fed. Cir. 1988)). Applicants therefore respectfully submit a rebuttal under each factor.

(1) Breadth of Claims: The claims in question are currently directed to methods of using human LXRα, which was known and described at the time the current specification was filed, to identify novel activators of the receptor. The currently pending claims specifically define the use of human LXRα, and reiterate the use of specific expression and reporter constructs.

(2) Absence or Presence of Working Examples: Applicants respectfully direct the Examiner's attention again to the experiments described on pages 16-26 and the drawings (Figures 1-5), which serve to demonstrate how to make and use the claimed methods. Therefore, the burden is now on the Examiner to show by preponderance of the evidence that the specification is non-enabling, as determined on the totality of the record.

(3) State of the Prior Art and Relative Skill of Those in the Art: In the experiments conducted with LXRα the Applicants have for the first time established that oxysterols are potentially important modulators metabolic function and that human LXRα is capable of regulation via small molecular weight ligands.

Importantly the present Applicants were the first to establish that human LXRα plays a role as a sensor of cholesterol metabolites, and could therefore be used in the context of drug discovery to identify novel modulators of the receptor.

(4) Amount of Direction or Guidance Presented and Quantity of Experimentation Necessary: Numerous expression and reporter constructed existed prior to the filing of the current specification, and the sequence of human LXRα, for example via GenBank, was available to a person of ordinary skill in the art without experimentation. See *In re Wright*, 27 USPQ 2d 1510 (Fed. Cir. 1993).

(5) Predictability or Unpredictability of the Art: The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required (see MPEP§ 2164.03). In response to Examiner's contention that the invention is highly unpredictable regarding the construction of LXRα expression cassettes Applicants respectfully point to the experimental sections outlining detailed descriptions of the cloning of suitable constructs.

(6) Nature of the Invention: Applicants respectfully direct the Examiner to Applicants' arguments under sections (1), (2), (3) and (4) to refute Examiner's claim, and reiterate that the specification does teach a person of ordinary skill in the art how to make and use the claimed inventions. Accordingly, it is Applicants position that based on the teachings of the specification, which the Examiner acknowledges enables practice of the claimed method with the disclosed species,

the ordinary skilled artisan would be able to make and use the claimed methods without undue experimentation.

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of pending claims 1, 4, 5, 7, 8, 17, 18, and 20-23 by the Board under 35 U.S.C. §112, first paragraph, since the specification is enabling for the claimed methods.

3. Rejections Under 35 U.S.C. §102

A. Willy et al.

The Examiner rejects all claims as anticipated by Willy *et al.* (Exhibit A). The Examiner alleges that since cholesterol and many oxysterols are the biochemical material for biosynthesis of retinoids, they are encompassed by the term oxysterol, and the Examiner further argues that the term "oxysterol" is unclear. Applicants respectfully disagree.

Cholesterol, and specifically oxysterols, are not precursors to retinoic acid, or involved in the synthesis of retinoic acid. By contrast, retinoic acid is formed from the pro-vitamin β–carotene, which is produced in plants and cannot be synthesized in mammalian cells. Accordingly retinoids cannot be considered to be encompassed within the term "oxysterol," even within the working definition proposed by the Examiner.

Secondly the term "oxysterol" defines a specific and art recognized group of compounds with clearly defined chemical and physical characteristics. Specifically, oxysterols encompass cholesterol derivatives with oxygenated side chains. These compounds are structurally and biosynthetically unrelated to the retinoids disclosed and used in Willey *et al.*

Thirdly prior to the Appellants' discovery that oxysterols were endogenous activators of LXR nuclear receptor, it was not known whether the nuclear receptor was responsive to small molecular weight ligands, or acted to regulate gene expression in a constitutive fashion. For example Willey *et al.* states:

> Thus far, our data support the notion that it is RXR and not LXR that binds the ligands used in these studies. It is also possible that the LXR/RXR heterodimer has unique ligand-binding properties that are different than either of the receptors alone, as is the case for the functional ecdysone receptor complex (Yao *et al.* 1993). Whether LXR also has a ligand is clearly an important area for further study. ***However, studies on both the known and orphan receptors have revealed that many of these proteins have transcription-modulating activity that may be considered ligand independent."***

Willey *et al.*, page 1042, first column lines 39 to 50 (emphasis added). Thus, Willey *et al.* neither discloses nor suggests ***any*** ligands that act specifically on LXR, rather Willey *et al.* teaches away from this possibility by suggesting that LXR may function in a ligand independent manner (*i.e.*, have high basal or constitutive transcriptional activity in the absence of a ligand).

Furthermore, Willey *et al.* does not teach that oxysterols are activators of LXR, and accordingly neither discloses nor suggests the step of treating a host cell with a candidate oxysterol activator of LXR mediated transcription, as reiterated in currently pending claims 1, 20 and 21. Because Willey *et al.* does not teach every element of the claimed methods it cannot anticipate the invention under 35 U.S.C. §102(b). Applicants accordingly request withdrawal of the rejection by the Board.

B. Hogness et al.

The Examiner also argues that all claims are anticipated by Hogness *et al.* (Exhibit B). The Examiner alleges that since ecdysteroids are oxysterols, the ecdysteroid

receptor disclosed by Hogness *et al.* is encompassed within the term "LXRα protein." The Examiner further alleges that the terms "LXRα expression construct," "LXRα protein," and "oxysterol activator" are not defined in terms of structure. Appellants respectfully disagree.

The terms in question are explicitly defined in the specification, and as discussed above, the metes and bounds of these terms would be clearly recognizable to one of ordinary skill in the relevant art. The insect Ecdysone receptor disclosed in Hogness *et al.* exhibits only approximately 39% amino acid identity with human LXRα within the ligand-binding domain, demonstrating that these proteins are not closely related. Also, as discussed above, an amendment to claims 1, 20 and 21 is offered reciting the use of a human LXRα expression construct and human LXR α protein.

Because Hogness *et al.* does not disclose nor suggest a human LXRα expression construct, nor the human LXRα protein, as recited in the claimed methods, it does not teach every element of the claimed inventions, and therefore cannot anticipate the claims under 35 U.S.C. §102(e). Applicants accordingly request withdrawal of the rejection by the Board.

C. Separate Patentability

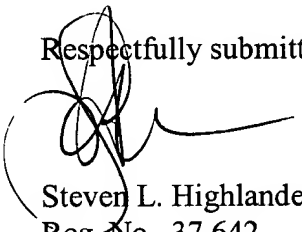
The examiner has rejected all claims as anticipate by either Willy or Hogness. Appellants submit that, with respect to Willy, the reference fails to describe an oxysterol is a derivative as set forth in either claim 17 or 21, and thus these claims (as well as 18 and 22, which depend therefrom respectively) are separately patentable over the cited art. With respect to Hogness, neither the expression constructs of claim 3, nor the mammalian

cells of claim 5 are described. In addition, the oxysterol derivatives of claims 17, 18, 20 and 21 are similarly not disclosed by Hogness. For these reason, these claims again are separately patentable over the reference.

X. Conclusion

It is respectfully submitted, in light of the above, that all claims are non-obvious over the cited art. Therefore, appellants request that the Board overturn each of the pending grounds for rejection.

Respectfully submitted,



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